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Optimization of extracorporeal shock wave lithotripsy delivery rates achieves excellent outcomes in ureteral stones. Results of a prospective, randomized trial.

Daniel P. Nguyen, MD [1,2], Stefanie Hnilicka, MD [1,2], Bernhard Kiss, MD [1], Roland Seiler, MD [1], George N. Thalmann, MD, Prof [1], Beat Roth, MD [1,3]

[1] Department of Urology, University of Bern, Bern, Switzerland
[2] Both authors contributed equally to the work
[3] Corresponding author

Corresponding author: Beat Roth, MD
Department of Urology
University Hospital Bern
CH - 3010 Bern
Switzerland
Phone number: +41 31 632 36 21
Fax number: +41 31 632 21 80
E-mail address: urology.berne@insel.ch

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Abstract

Purpose: Management of ureteral stones remains controversial. To determine whether optimizing extracorporeal shock wave lithotripsy (ESWL) delivery rates improves treatment of solitary ureteral stones, we compared outcomes of two SW delivery rates in a prospective, randomized trial**.**

Materials and Methods: From July 2010 to October 2012, 254 consecutive patients were randomized to undergo ESWL at SW delivery rates of either 60 pulses (n=130) or 90 pulses (n=124) per min. The primary endpoint was stone-free rate at 3-month follow-up. Secondary endpoints included stone disintegration, treatment time, complications, and the rate of secondary treatments. Descriptive statistics were used to compare endpoints between the two groups. Adjusted odds ratios and 95% confidence intervals were calculated to assess predictors of success.

Results: The stone-free rate at 3 months was significantly higher in patients who underwent ESWL at a SW delivery rate of 90 pulses per min than in those receiving 60 pulses (91% vs. 80%, p=0.01). Patients with proximal and mid-ureter stones, but not those with distal ureter stones, accounted for the observed difference (100% vs. 83%; p=0.005; 96% vs. 73%, p=0.03; and 81% vs. 80%, p=0.9, respectively). Treatment time, complications, and the rate of secondary treatments were comparable between the two groups. In multivariable analysis, SW delivery rate of 90 pulses per min, proximal stone location, stone density, stone size and the absence of an indwelling JJ stent were independent predictors of success.

Conclusions: Optimization of ESWL delivery rates can achieve excellent results for ureteral stones.

Introduction

Extracorporeal shock-wave lithotripsy (ESWL) for stone disease using the Dornier HM-3 lithotripter (Dornier MedTech, Wessling, Germany) was introduced more than 30 years ago (1). Since then improvements in shock-wave (SW) technology have been minimal, and current devices fail to match the efficacy of the Dornier HM-3 (2–4). During this time endourological procedures, which offer the possibility of one-time complete clearance, have become increasingly popular. Nevertheless, ESWL, along with ureterorenoscopy (URS), remains an accepted treatment for urolithiasis, including stones located in the ureter (5). In fact, depending on stone location and size, ESWL may be the better option, with the advantage of being a noninvasive procedure.

Recent research has focused on finding ways to make ESWL more effective. Optimizing lithotripter setting parameters, notably SW delivery rates, has been shown to possibly improve treatment outcomes (6). Several studies evaluated the impact of SW delivery rates on stone clearance in kidney stones comparing SW delivery rates of 60 versus 120 pulses per min (7–11). Most of these studies (7–10) reported better success rates in kidney stones with the lower SW delivery rate of 60 pulses per min. A recent meta-analysis of randomized trials found that SW delivery rates of 60 and 90 pulses per minute yield better results than higher frequencies, but suggested that 90 pulses per minute may be the optimal SW delivery rate because of the shorter treatment duration (12). To extend these observations in the setting of ureteral stone disease, and especially since data on the impact of SW delivery rates on ESWL efficacy in ureteral stones are sparse and inconsistent (10,13,14), we conducted a large prospective, randomized trial comparing ESWL efficacy at 60 versus 90 pulses per min using the modified Dornier HM-3 for solitary ureteral stones.

Material and Methods

A total of 260 patients (207 males and 53 females) ≥ 18 years of age with previously untreated, unilateral radiopaque ureteral stones requiring elective or emergency ESWL were recruited from July 2010 to October 2012 at our department. Patients in whom it was technically impossible to localize the stone (e.g. due to patient obesity) on the day of intervention (n=4), or who refused to participate (n=2) were excluded. Upon entry into the study, each patient was randomly assigned by a computer-based program without stratification to receive ESWL at a SW delivery rate of 60 pulses (group A, n=130) or 90 pulses (group B, n=124) per min. Fourteen of these patients were excluded from analysis due to loss to follow-up (Group A: n=3; group B: n=11; Fig.1). Patient baseline and stone characteristics were comparable between the two groups (Table 1). The study protocol was approved by the Ethics Committee of the Canton Bern, Switzerland (protocol number 089/10). All patients provided informed written consent to participate in the study prior to randomization.

a) Preoperative assessment

Preoperative 12-lead ECGs were performed on all patients with 2 or more cardiovascular risk factors (arterial hypertension, hypercholesterolemia, history of smoking, body mass index [BMI] ≥ 30 kg/m², diabetes), history of subarachnoidal bleeding, or systemic disease with potential cardiac involvement. ECGs were interpreted by a cardiologist and reviewed by an anesthesiologist. None of the patients had active coronary heart disease, a history of cardiac surgery, severe pretreatment cardiac arrhythmias, or other significant cardiac symptoms or signs. Had there been such patients, they would have been excluded from the study to ensure patient safety from a cardiovascular standpoint as the ESWL treatment included potential pharmacological manipulation to regulate heart rate (see below).

b) ESWL protocol

The technical features of the modified Dornier HM3 are described elsewhere (2). The Dornier HM-3 was operated by the same technician with more than 25 years of experience at the start of the study, under the supervision and guidance of a specially-trained resident and a senior staff member (2). All ESWL treatments were given under anesthesia (general or regional) to eliminate pain as a limiting factor and to keep respiratory movements regular (Table 1). SW delivery was ECG gated. If necessary, patients underwent pharmacological manipulation with atropine/hyoscine butylbromide or esmolol to maintain the required heart rate/SW delivery rate.

SW voltage began with a series of 500 SWs at 19 kV, thereafter it was increased in 1-kV steps every 300 SWs to a maximum of 21kV to 22kV if fluoroscopic controls showed insufficient fragmentation. In case of stone disintegration, voltage was progressively decreased to prevent unnecessary trauma (9). A maximum of 2500 SWs for proximal ureteral stones and 3000 SWs for ureteral stones off the kidney were administered. ESWL was terminated prior to reaching the maximum number of SWs upon documentation of complete fragmentation on x-ray snapshots. All patients were given α-blockers after ESWL.

c) Outcome measures

Kidney, ureter and bladder x-rays and renal ultrasound were obtained 1 day and 3 months after ESWL. Additional imaging (x-ray, renal ultrasound, computed tomography and/or excretory urography) was only used if deemed necessary in order to reduce exposure to ionizing radiation and to limit costs. Stone disintegration was classified as no fragments, fragments <2 mm, fragments 2mm to 5 mm, and fragments >5 mm. Complications and secondary treatments were prospectively evaluated. Stone composition was documented if available. The investigators who assessed clinical outcomes were blinded to patient treatment information.

d) Study endpoints and statistical analyses

The primary study endpoint was success rate 3 months following ESWL, defined as the stone-free rate after a single ESWL session, i.e. without the need for secondary treatment. Secondary endpoints were stone disintegration, treatment time, complications (Clavien-Dindo classification) including kidney hematoma, and the rate of secondary treatments, which included re-ESWL, placement of a JJ stent, percutaneous nephrolithotomy, and URS.

Based on the assumption that the overall drop-out rate would be 10% and that the stone-free rate at 3 months would be 90% after treatment with 60 SWs per min and 78% after 90 SWs per min, a sample size of 254 patients (n=127 per group) was needed to obtain a statistical power of 80% (β=0.2) using a two-sided test at the significance level of 5% (α=0.05). Categorical and continuous variables were compared using the $\chi 2$ and Mann-Whitney U tests, respectively. A two-tailed p value <0.05 was considered significant. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated in a logistic regression model to assess predictors of treatment success. Confounders with a univariate significance level of ≤ 10% ($\alpha \leq 0.1$) were included in multivariable analyses (SW delivery rate, stone location, stone density measured in Hounsfield units, stone size, and presence of an indwelling JJ stent). Statistics were performed using SAS 9.1 software (SAS Institute Inc., Cary, NC).

Results

The stone-free rate at 3-month follow-up was significantly higher in patients who underwent ESWL at a SW delivery rate of 90 pulses per min than at 60 pulses per min (103/113 [91%] vs. 101/127 patients [80%], p=0.01). Patients with proximal and mid-ureter stones, but not those with distal ureter stones, accounted for the observed difference (Table 2). Similarly, stone disintegration was better at 90 pulses per min (p=0.04). Treatment time and complications were comparable between the two groups (Table 2). Sixteen of 127 (13%) patients in group A (60 SW per min) and 7 of 113 (6%) patients in group B (90 SW per min) required a secondary treatment (p=0.06; Table 2). Stone analysis was available in 75 of 127 (59%) patients in group A and 81 of 113 (72%) patients in group B. The distribution of stone composition in these patients did not differ between the two groups (p = 0.09; Fig. 2).

Multivariable logistic regression analysis showed an association between treatment success and SW delivery rate in favor of a frequency of 90 pulses per min (OR: 0.43, 95% CI 0.19-0.96, p=0.02; Table 3). Other predictors of success were proximal stone location, lower stone density, smaller stone size, and the absence of an indwelling JJ stent. Because patient age, gender, and BMI were not associated with treatment success in univariate analysis (p > 0.1), these variables were not included in the logistic regression model.

Discussion

Classical variables that determine ESWL success rates include stone burden, stone composition and location, level of operator experience, and the type of lithotripter used. The last decade has seen an increasing interest in improving success rates by manipulating lithotripter setting parameters, which include maximal voltage, voltage escalation, and SW delivery rate (6). In the present prospective, randomized study using the “Rolls-Royce” among lithotripters, the Dornier HM-3 to treat ureteral stones, we show that SW delivery rates of 90 pulses per min are associated with significantly better treatment outcomes than SW delivery rates of 60 pulses per min. Rates of 90 pulses per min delivered an overall stone-free rate of 91% and, for mid-ureter and proximal ureteral stones, stone-free rates of >95%. These findings are relevant in the context of the declining popularity of ESWL for ureteral stones, indicating that optimizing the SW delivery rate can achieve excellent outcomes even for mid-ureter and proximal ureteral stones.

As newer lithotripters emerged, an increased interest in shorter ESWL treatment times led to several randomized trials designed to evaluate the potential role of SW delivery rates. Based on manufacturers’ recommended SW delivery rates in second- and third-generation devices, the majority of these studies compared frequencies of 60 pulses per min versus 120 pulses (6–11,13). Although not without limitations, such as lack of control over the number of ESWL sessions (10) or overall low success rates regardless of SW delivery rate (7,8,13), the majority of these studies reported higher success rates at a SW delivery rate of 60 pulses per min. Honey et al specifically investigated upper ureteral stones only and found improved outcomes at a SW delivery rate of 60 versus 120 pulses per min (13), with stone-free rates at 3-month follow-up of 64.9% and 48.8%, respectively. Conversely, Robert et al reported success rates of 65% and 89% for lower ureteral stones ($p = 0.04$) at SW delivery rates of 60 and 240 pulses per min, respectively (14). In the present study, we chose to evaluate the modified Dornier HM-3 because it remains the gold standard against which treatment outcomes with other lithotripters are compared. In addition, we included only patients with ureteral stones. Indeed, while ESWL efficacy for renal stones is well documented (2–4), management of ureteral stones remains controversial, as ESWL and primary URS represent equally popular treatment options (5). Although we achieved acceptable results at the lower SW delivery rate of 60 pulses per min, more than 9 of 10 patients receiving 90 pulses per min were stone-free at 3 months. Our results compare favorably with those of studies evaluating new-generation lithotripters, in which stone-free rates after a single ESWL session for ureteral stones ranged from 57% to 82% (13–15). In recent years these mixed results, combined with advances in endourological techniques, have prompted many urologists to turn to primary URS for ureteral stone removal.

The reasons for the superior ESWL efficacy at 90 pulses per min may be related to favorable cavitation bubble dynamics. Shock waves create pressure changes that lead to bubble formation (16). When these bubbles collapse at the stone surface, they release high-energy waves that induce stone fragmentation (17). An increased SW delivery rate leads to increased production of cavitation bubbles at the stone surface (16), potentially leading to enhanced fragmentation. On the other hand, residual bubbles that are not reflected on the stone and that do not dissipate before the arrival of the next SW may act as a barrier that attenuates SW energy transmission (16). It has also been postulated that stone particles that persist between SWs can serve as cavitation nuclei. The resulting bubble growth may absorb part of the energy from the negative-pressure phase of the SW, ultimately reducing stone breakage (18). These two theories have been advanced to explain why low success rates were observed at SW delivery rates of 120 pulses per min (16,18). Therefore, a SW delivery rate of 90 pulses per min may provide the optimal balance by supporting favorable cluster bubble dynamics on the stone surface while allowing enough time for the barrier of residual bubbles or stone particles to dissipate. A SW delivery rate of 90 pulses per min may also enhance stone fatigue, which is another postulated mechanism of stone breakage (19,20).

Among the secondary findings of our study, stone location was shown to be a predictive factor for treatment success, success being significantly associated with proximal ureteral stones as reported previously (15,21). Reduced stone fragmentation in the lower ureter may reflect attenuation of SW energy by the organic environment surrounding the stone, i.e. abdominal gas interposition and/or an energy absorptive effect of the bony pelvis and muscle mass of the buttocks (19). Moreover, fluoroscopic focusing in the pelvis may be more difficult due to fecal air and content and/or projection in front of the sacroiliac joint. Another possible explanation is the smaller fluid interface surrounding the stone in the lower ureter (22). Despite this, we and others have previously reported stone-free rates >90% for distal ureteral calculi (23,24), and, in the current study, 82 of 102 patients (80.4%) with distal ureteral stones were stone-free 3 months after ESWL. Therefore, stone location in the lower ureter does not necessarily preclude the use of ESWL as a primary treatment option.

We also found that the presence of an indwelling JJ stent reduced the chance of treatment success. These findings echo those of previous studies (15,21). The magnitude of SW transmission and reflection travelling to the stone depends on the acoustic impedance of the intervening structures (19). Thus, lower success rates in stented patients may result from partial SW absorption by the ureteral stent. It has also been shown that stents impair ureteric peristalsis and/or trap larger stone fragments, thereby reducing stone clearance (25). Nevertheless, JJ stents are still needed for patients in the emergency setting or receiving treatment outside referral centers, where lithotripters are not readily available. Other predictors of outcome were stone size and density, which are generally accepted factors affecting ESWL treatment outcomes (8,10,15,21,26,27). BMI was not associated with outcomes in our patients. This finding accords with a recent study that found BMI and skin-to-stone distance to have no effect on ESWL efficacy with the Dornier HM-3 (28). Regarding newer lithotripters and BMI, some authors report an association between BMI and treatment outcomes (21,26) and some do not (7,13).

The main limitation of our study is that all patients were treated with the modified Dornier HM-3. It is unknown, therefore, whether our results can be generalized to the current generation of electromagnetic or piezoelectric lithotripters. The optimal SW delivery rate may vary depending on the type of device

Conclusions

Excellent outcomes of ESWL for ureteral stones can be achieved by optimizing the SW delivery rate, especially for stones located more proximally. Our results should encourage other high-volume centers to design similar studies to determine optimal treatment parameters for the most commonly used lithotripters.

Conflicts of interest and financial disclosures

There was no financial support or funding for this study, and there is no conflict of interest.

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Table 1 - Patient and stone characteristics

	Group A (60 SWs per min) n=127	Group B (90 SWs per min) n=113	p-value
Median age (years; range)	48 (18-84)	49 (19-84)	0.9 [1]
Median BMI (range)	25.6 (17-61.7)	26.6 (17.9-36.5)	0.2 [1]
Gender, no (%)			0.3 [2]
male	103 (81)	86 (76)	
female	24 (19)	27 (24)	
Anesthesia, no (%)			0.1 [2]
PDA	52 (41)	46 (41)	
GA	12 (9)	19 (17)	
Spinal single shot	63 (50)	48 (42)	
JJ in place, no (%)			0.4 [2]
no	96 (76)	91 (81)	
yes	31 (24)	22 (19)	
Stone size, no (%)			0.3 [2]
< 5 mm	37 (29)	39 (35)	
5 – 10 mm	65 (51)	60 (53)	
10 – 20 mm	22 (17)	14 (12)	
> 20 mm	3 (2)	0 (0)	
Stone location, no (%)			0.7 [2]
proximal ureter	42 (33)	43 (38)	
midureter	30 (24)	23 (20)	
distal ureter	55 (43)	47 (42)	
Stone density, no (%)			0.2 [2]
< 500 HU	9 (7)	8 (7)	
500 - 1000 HU	83 (65)	81 (72)	
> 1000 HU	35 (28)	24 (21)	
Mean no. of SW applied (SD)	**2381 (745)**	**2401 (550)**	0.5 [1]

Abbreviations:

Table 2 - Outcomes

	Group A (60 SWs per min) n=127	Group B (90 SWs per min) n=113	p-value
Stone free rate at 3 mos, no (%)	101 (80)	103 (91)	0.01 [1]
Proximal ureter	35 (83)	43 (100)	0.005[1]
Midureter	22 (73)	22 (96)	0.03 [1]
Distal ureter	44 (80)	38 (81)	0.9[1]
Stone disintegration, no (%)			0.04 [1]
No fragments	100 (79)	103 (91)	
0-2 mm	12 (9)	4 (4)	
2-5 mm	6 (5)	3 (3)	
> 5 mm	9 (7)	3 (3)	
Treatment time, min, mean (SD)	36.4 (13.6)	35.3 (9.4)	0.9 [2]
Complications, no (%)	13 (10)	17 (15)	0.2 [1]
Grade 1	6 (5)	4 (4)	
Grade 2	2 (2)	1 (1)	
Grade 3a	0 (0)	0 (0)	
Grade 3b	1 (1)	5 (4)	
Grade 4a	4 (3)	7 (6)	
Grade 4b	0 (0)	0 (0)	
Grade 5	0 (0)	0 (0)	
Kidney hematomas, no (%)	3 (2)	1 (1)	0.3 [1]
Secondary treatment, no (%)	16 (13)	7 (6)	0.06 [1]
Re-ESWL	10 (8)	1 (1)	
JJ stent	2 (2)	1 (1)	
Percutaneous nephrolithotomy	0 (0)	0 (0)	
Ureterorenoscopy	4 (3)	5 (4)	

[1] Chi square test [2] Mann Whitney test

Table 3 - Multivariate regression analysis of treatment success in relation to treatment parameters, and stone characteristics

	p value	**OR (95% CI)**
SW delivery rate	0.02	0.43 (0.19-0.96)
Stone location	0.008	4.96 (1.69-16.83)
Stone density	0.0003	0.23 (0.1-0.49)
Stone size	0.0008	0.62 (0.52-0.77)
JJ	0.03	0.96 (0.93-0.99)

Abbreviations: SW = shock wave; JJ = Double-J stent; OR = odds ratio

Figure 1

CONSORT diagram enumerating the patients screened, randomized, allocated to each treatment arm, lost to follow up, and included in the final analysis.

Figure 2

Distribution of stone composition. Stone analysis could be obtained in 75/127 (59%) of group A patients and 81/113 (72%) of group B patients.

Fig. 1

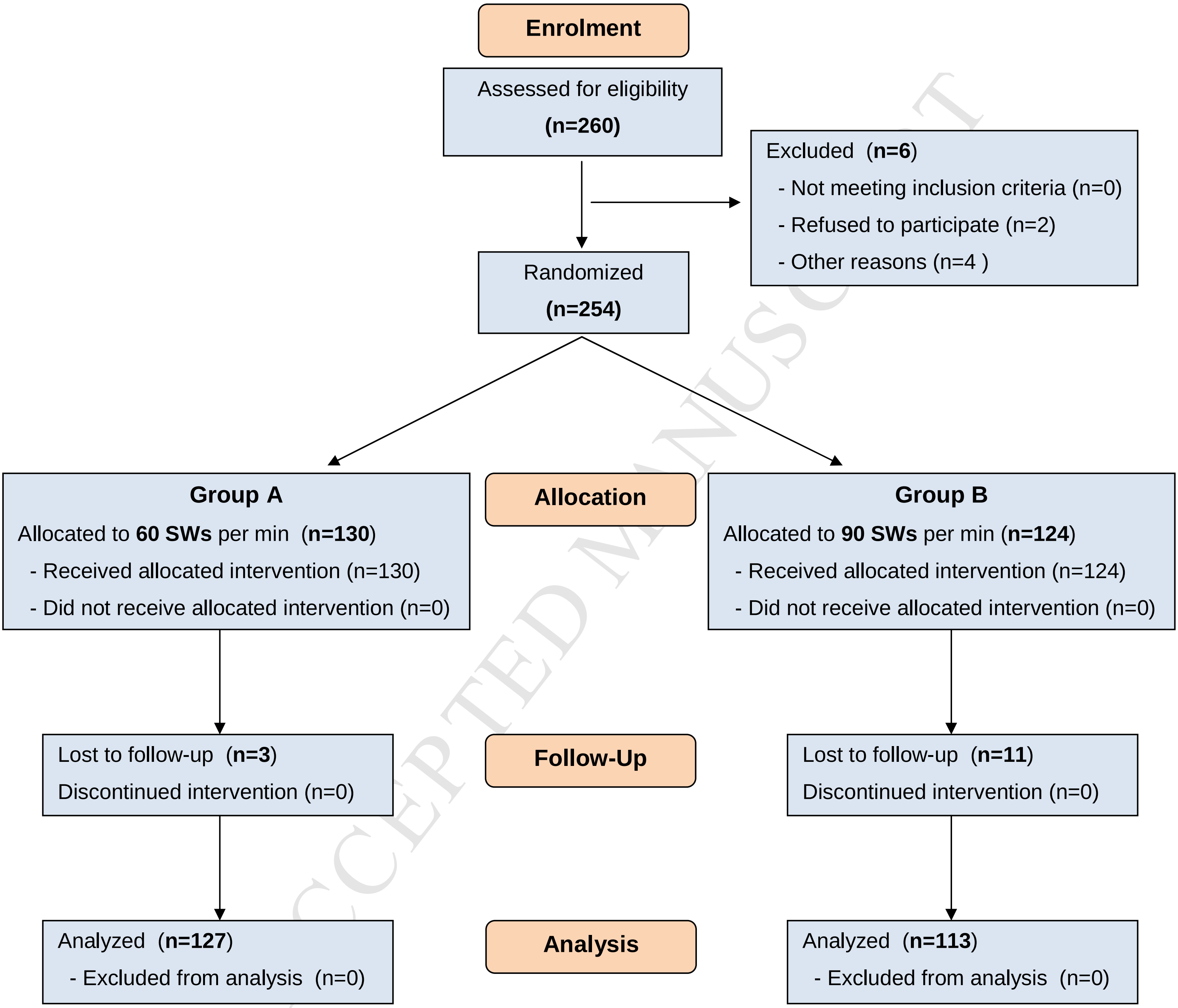
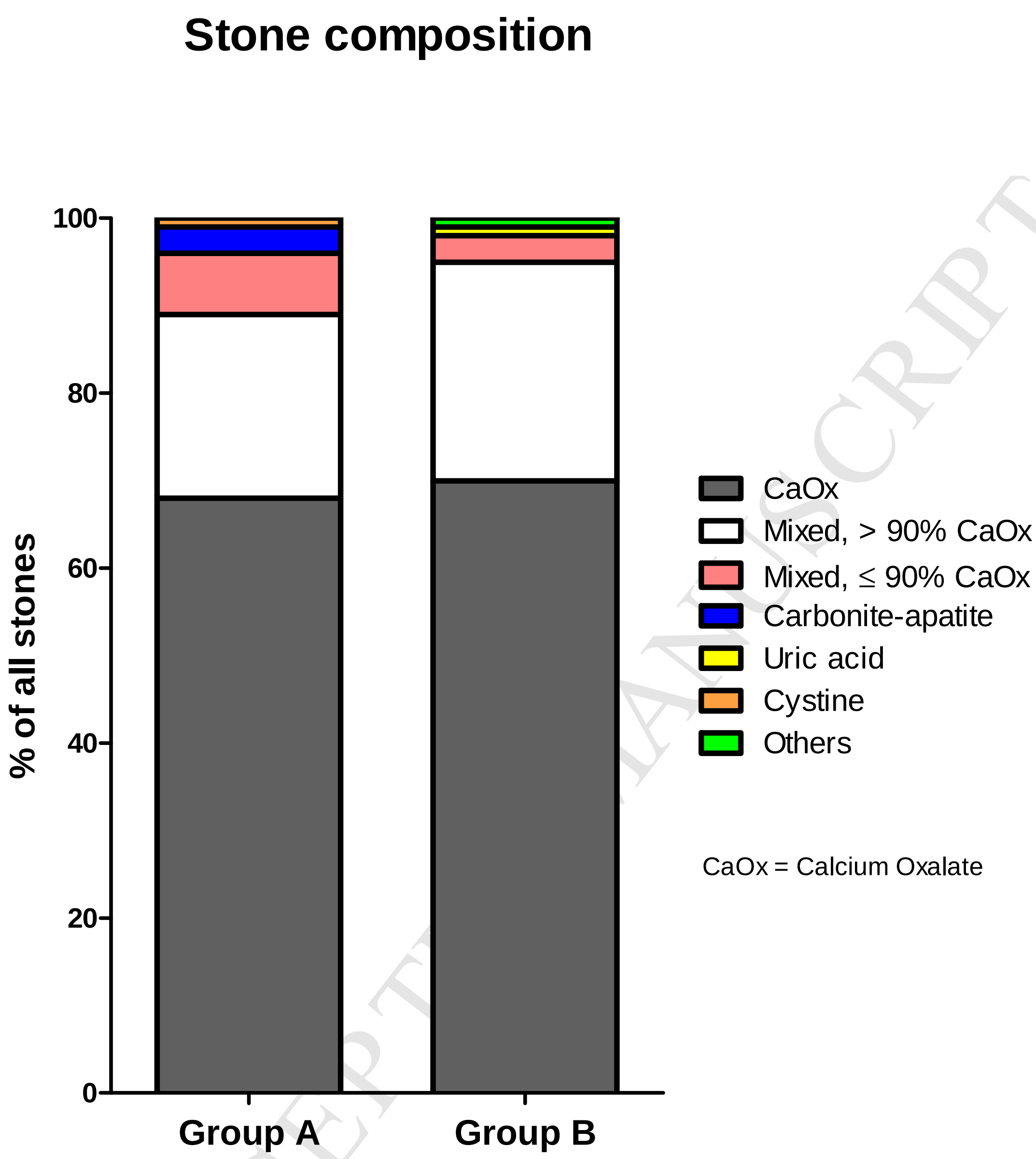

Enrolment
Assessed for eligibility (n=260)
Excluded (n=6)
- Not meeting inclusion criteria (n=0)
- Refused to participate (n=2)
- Other reasons (n=4)
Randomized (n=254)
Group A
Allocated to 60 SWs per min (n=130)
- Received allocated intervention (n=130)
- Did not receive allocated intervention (n=0)
Allocation
Group B
Allocated to 90 SWs per min (n=124)
- Received allocated intervention (n=124)
- Did not receive allocated intervention (n=0)
Lost to follow-up (n=3)
Discontinued intervention (n=0)
Follow-Up
Lost to follow-up (n=11)
Discontinued intervention (n=0)
Analyzed (n=127)
- Excluded from analysis (n=0)
Analysis
Analyzed (n=113)
- Excluded from analysis (n=0)

Fig. 2



Stone composition
% of all stones
100
80
60
40
20
0
Group A
Group B
CaOx
Mixed, > 90% CaOx
Mixed, ≤ 90% CaOx
Carbonite-apatite
Uric acid
Cystine
Others
CaOx = Calcium Oxalate

Key of definitions and abbreviations

ESWL	extracorporeal shock wave lithotripsy
JJ stent	double J stent
SW	shock wave
URS	ureterorenoscopy